

## CLAIMS

We claim:

1. An isolated polypeptide of at least 15 amino acid residues comprising an epitope-bearing portion of a protein of SEQ ID NO:2.

2. The polypeptide of claim 1 wherein said polypeptide comprises a segment that is at least 70% identical to a sequence selected from the group consisting of:

- (a) residues 52-179 of SEQ ID NO:2; and
- (b) residues 258-370 of SEQ ID NO:2.

3. The isolated polypeptide according to claim 1 wherein said polypeptide is selected from the group consisting of:

- residues 19-179 of SEQ ID NO:2;
- residues 52-179 of SEQ ID NO:2;
- residues 19-253 of SEQ ID NO:2;
- residues 52-253 of SEQ ID NO:2;
- residues 19-255 of SEQ ID NO:2;
- residues 52-255 of SEQ ID NO:2;
- residues 19-257 of SEQ ID NO:2;
- residues 52-257 of SEQ ID NO:2;
- residues 19-253 of SEQ ID NO:2;
- residues 52-253 of SEQ ID NO:2;
- residues 19-370 of SEQ ID NO:2;
- residues 52-370 of SEQ ID NO:2;
- residues 180-370 of SEQ ID NO:2; and
- residues 258-370 of SEQ ID NO:2.

4. An isolated polypeptide comprising a sequence of amino acids of the formula  $R1_x-R2_y-R3_z$ , wherein:

R1 is a polypeptide of from 100 to 130 residues in length, is at least 70% identical to residues 52-179 of SEQ ID NO:2, and comprises a sequence motif C[KR]Y[DNE][WYF]X{11,15}G[KR][WYF]C (SEQ ID NO:4) corresponding to residues 109-131 of SEQ ID NO:2;

R2 is a polypeptide at least 90% identical to residues 180-257 of SEQ ID NO:2;

R3 is a polypeptide at least 70% identical in amino acid sequence to residues 258-370 of SEQ ID NO:2 and comprises cysteine residues at positions corresponding to residues 272, 302, 306, 318, 360, and 362 of SEQ ID NO:2; a glycine residue at a position corresponding to residue 304 of SEQ ID NO:2; and a sequence motif CX{18,33}CXGXCX{6,33}CX{20,50}CXC (SEQ ID NO:3) corresponding to residues 272-362 of SEQ ID NO:2; and

each of x, y, and z is individually 0 or 1, subject to the limitations that:  
at least one of x and z is 1; and  
if x and z are each 1, then y is 1.

5. The isolated polypeptide of claim 4 wherein x=1.

6. The isolated polypeptide of claim 5 wherein R1 is at least 90% identical to residues 52-179 of SEQ ID NO:2.

7. The isolated polypeptide of claim 5 wherein R1 comprises residues 52-179 of SEQ ID NO:2.

8. The isolated polypeptide of claim 5 wherein R1 is at least 90% identical to residues 19-179 of SEQ ID NO:2.

9. The isolated polypeptide of claim 5 wherein y=1.

10. The isolated polypeptide of claim 9 wherein z=1.

11. The isolated polypeptide of claim 10 wherein R3 is at least 90% identical to residues 258-370 of SEQ ID NO:2.

12. The isolated polypeptide of claim 4 wherein said polypeptide comprises residues 52-253 of SEQ ID NO:2, residues 180-370 of SEQ ID NO:2, or residues 52-370 of SEQ ID NO:2.

13. The isolated polypeptide of claim 4 wherein z=1.

14. The isolated polypeptide of claim 13 wherein R3 is at least 90% identical to residues 258-370 of SEQ ID NO:2.

15. The isolated polypeptide of claim 13 wherein R3 comprises residues 258-370 of SEQ ID NO:2.

16. The isolated polypeptide of claim 13 wherein  $y=1$ .

17. The isolated polypeptide of claim 16 wherein  $x=1$  and R1 is at least 90% identical to residues 52-179 of SEQ ID NO:2.

18. The isolated polypeptide of claim 17 wherein R3 is at least 90% identical to residues 258-370 of SEQ ID NO:2.

19. The isolated polypeptide of claim 13, further comprising cysteine residues at positions corresponding to residues 308 and 316 of SEQ ID NO:2.

20. The isolated polypeptide of claim 4, further comprising an affinity tag.

21. The isolated polypeptide of claim 4, further comprising an immunoglobulin constant domain.

22. An isolated protein comprising a first polypeptide operably linked to a second polypeptide, wherein said first polypeptide comprises a sequence of amino acids of the formula  $R1_x-R2_y-R3_z$ , wherein:

R1 is a polypeptide of from 100 to 130 residues in length, is at least 70% identical to residues 52-179 of SEQ ID NO:2, and comprises a sequence motif  $C[KR]Y[DNE][WYF]X\{11,15\}G[KR][WYF]C$  (SEQ ID NO:4) corresponding to residues 109-131 of SEQ ID NO:2;

R2 is a polypeptide at least 90% identical to residues 180-257 of SEQ ID NO:2;

R3 is a polypeptide at least 70% identical in amino acid sequence to residues 258-370 of SEQ ID NO:2 and comprises cysteine residues at positions corresponding to residues 272, 302, 306, 318, 360, and 362 of SEQ ID NO:2; a glycine residue at a position corresponding to residue 304 of SEQ ID NO:2; and a sequence motif  $CX\{25,33\}CXGXCX\{10,33\}CX\{20,50\}CXC$  (SEQ ID NO:3) corresponding to residues 272-362 of SEQ ID NO:2; and

each of  $x$ ,  $y$ , and  $z$  is individually 0 or 1, subject to the limitations that:

at least one of  $x$  and  $z$  is 1; and

if  $x$  and  $z$  are each 1, then  $y$  is 1,

and wherein said protein modulates cell proliferation, apoptosis, differentiation, metabolism, or migration.

23. The isolated protein of claim 22 wherein said protein is a heterodimer.

24. The isolated protein of claim 23 wherein  $z$  is 1 and said second polypeptide is selected from the group consisting of VEGF, VEGF-B, VEGF-C, VEGF-D, zveg3, PlGF, PDGF-A, and PDGF-B.

25. The isolated protein of claim 23 wherein:

$x=1$ ,  $z=1$ , and said second polypeptide comprises residues 46-345 of SEQ ID

NO:32;

$x=1$  and said second polypeptide comprises residues 46-170 of SEQ ID

NO:32; or

$z=1$  and said second polypeptide comprises residues 235-345 of SEQ ID

NO:32.

26. The isolated protein of claim 22 wherein said protein is a homodimer.

27. The isolated protein of claim 26 wherein  $z=1$ .

28. The isolated protein according to claim 27 wherein each of said first and second polypeptides comprises residues 258-370 of SEQ ID NO:2.

29. The isolated protein of claim 26 wherein  $x=1$ .

30. The isolated protein of claim 29 wherein each of said first and second polypeptides comprises residues 52-179 of SEQ ID NO:2.

31. An isolated protein produced by a method comprising:

(a) culturing a host cell containing an expression vector comprising the following operably linked elements:

a transcription promoter;

a DNA segment encoding a polypeptide comprising a sequence of amino acid residues selected from the group consisting of:

i) residues 52-370 of SEQ ID NO:2;

ii) residues 52-253 of SEQ ID NO:2;

- iii) residues 180-370 of SEQ ID NO:2; and
- iii) residues 258-370 of SEQ ID NO:2; and
- a transcription terminator,
- under conditions whereby the DNA segment is expressed; and
- (b) recovering from the cell the protein product of expression of the DNA

construct.

32. An isolated polynucleotide of up to approximately 4.4 kb in length, wherein said polynucleotide encodes a polypeptide comprising a sequence of amino acids of the formula  $R1_x-R2_y-R3_z$ , wherein:

R1 is a polypeptide of from 100 to 130 residues in length, is at least 70% identical to residues 52-179 of SEQ ID NO:2, and comprises a sequence motif  $C[KR]Y[DN]E[WYF]X\{11,15\}G[KR][WYF]C$  (SEQ ID NO:4) corresponding to residues 109-131 of SEQ ID NO:2;

R2 is a polypeptide at least 90% identical to residues 180-257 of SEQ ID NO:2;

R3 is a polypeptide at least 70% identical in amino acid sequence to residues 258-370 of SEQ ID NO:2 and comprises cysteine residues at positions corresponding to residues 272, 302, 306, 318, 360, and 362 of SEQ ID NO:2; a glycine residue at a position corresponding to residue 304 of SEQ ID NO:2; and a sequence motif  $CX\{25,33\}CXGXCX\{10,33\}CX\{20,50\}CXC$  (SEQ ID NO:3) corresponding to residues 272-362 of SEQ ID NO:2; and

- each of x, y, and z is individually 0 or 1, subject to the limitations that:
- at least one of x and z is 1; and
- if x and z are each 1, then y is 1.

33. The polynucleotide of claim 32, wherein said polynucleotide is DNA.

34. The polynucleotide of claim 33 comprising nucleotides 1 through 1110 of SEQ ID NO:6.

35. The polynucleotide of claim 33 comprising nucleotides 226 through 1335 of SEQ ID NO:1.

36. An expression vector comprising the following operably linked elements:

- a transcription promoter;

a DNA polynucleotide according to claim 32; and  
a transcription terminator.

37. The expression vector of claim 36, further comprising a secretory signal sequence operably linked to the DNA polynucleotide.

38. A cultured cell into which has been introduced an expression vector according to claim 36, wherein said cell expresses the polypeptide encoded by the DNA polynucleotide.

39. A pharmaceutical composition comprising a protein according to claim 22 in combination with a pharmaceutically acceptable vehicle.

40. The pharmaceutical composition of claim 39 wherein  $x=1$ .

41. The pharmaceutical composition of claim 39 wherein  $z=1$ .

42. A method of producing a protein comprising:  
culturing a cell into which has been introduced an expression vector according to claim 36, whereby said cell expresses the polypeptide encoded by the DNA segment; and  
recovering the expressed protein.

43. An antibody that specifically binds to an epitope of a polypeptide according to claim 4.

44. The antibody of claim 43 which is a monoclonal antibody.

45. The antibody of claim 43 which is a single-chain antibody.

46. The antibody of claim 43 operably linked to a reporter molecule.

47. A method for detecting a genetic abnormality in a patient, comprising:  
obtaining a genetic sample from a patient;  
incubating the genetic sample with a polynucleotide comprising at least 14 contiguous nucleotides of SEQ ID NO:1 or the complement of SEQ ID NO:1, under conditions wherein said polynucleotide will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and

comparing said first reaction product to a control reaction product, wherein a difference between said first reaction product and said control reaction product is indicative of a genetic abnormality in the patient.

48. A polypeptide comprising a sequence selected from the group consisting of:  
residues 46-234 of SEQ ID NO:33 operably linked to residues 258-370 of SEQ ID NO:2;  
residues 46-170 of SEQ ID NO:33 operably linked to residues 180-370 of SEQ ID NO:2;  
residues 52-257 of SEQ ID NO:2 operably linked to residues 235-345 of SEQ ID NO:33; and  
residues 52-179 of SEQ ID NO:2 operably linked to residues 171-345 of SEQ ID NO:33.

49. A method of activating a cell-surface PDGF receptor, comprising exposing a cell comprising a cell-surface PDGF receptor to the polypeptide or protein of any of claims 1-31, whereby the polypeptide or protein binds to and activates the receptor.

50. The method of claim 49 wherein the receptor is a PDGF alpha-receptor.

51. The method of claim 49 wherein the receptor is a PDGF beta-receptor.

52. A method of inhibiting a PDGF receptor mediated cellular process, comprising exposing a cell comprising a cell-surface PDGF receptor to a compound that inhibits binding of the polypeptide or protein of any of claims 1-31 to the receptor.

53. A method of stimulating the growth of bone tissue, comprising applying to bone a growth-stimulating amount of the polypeptide or protein of any of claims 1-31.

54. A method of modulating the proliferation, differentiation, migration, or metabolism of bone cells, comprising exposing bone cells to an effective amount of the polypeptide or protein of any of claims 1-31.